

FIGURE 1

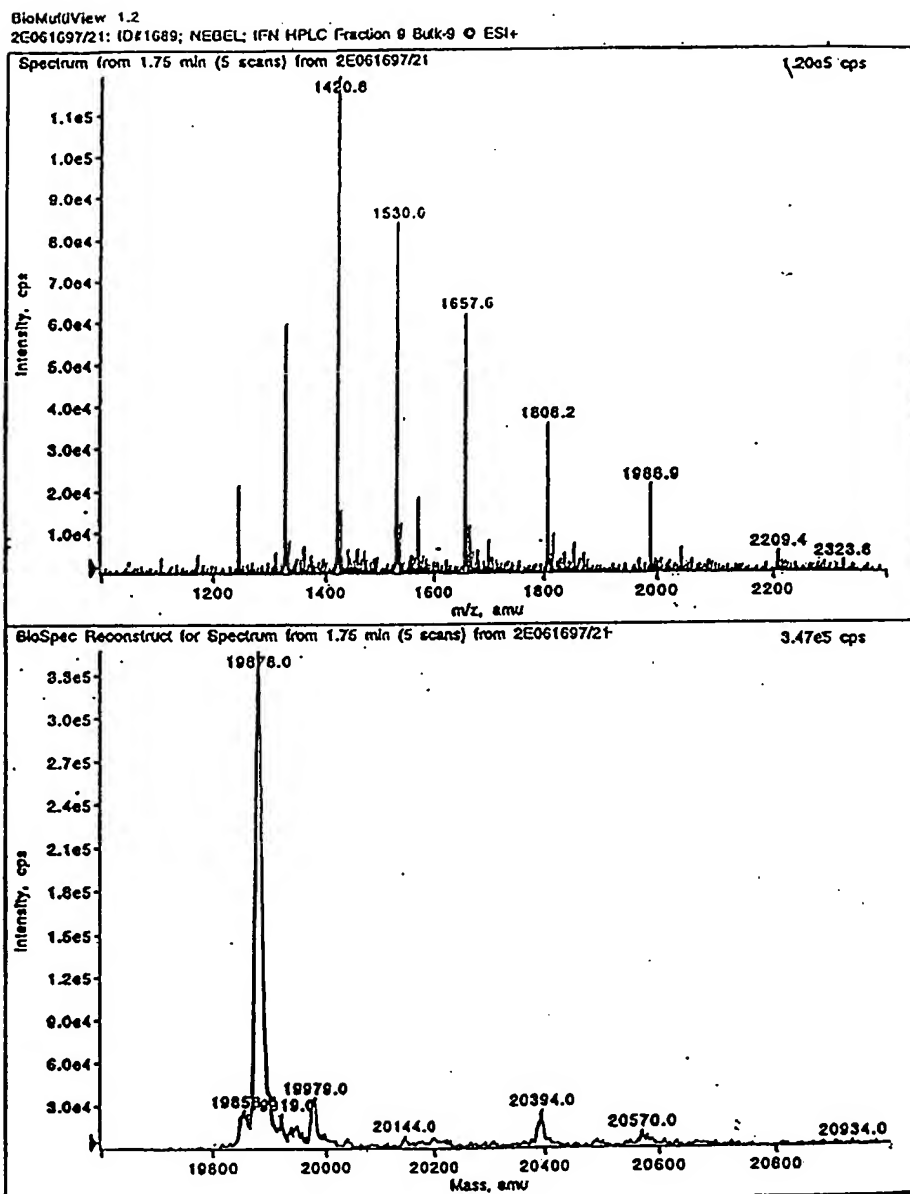


FIGURE 2

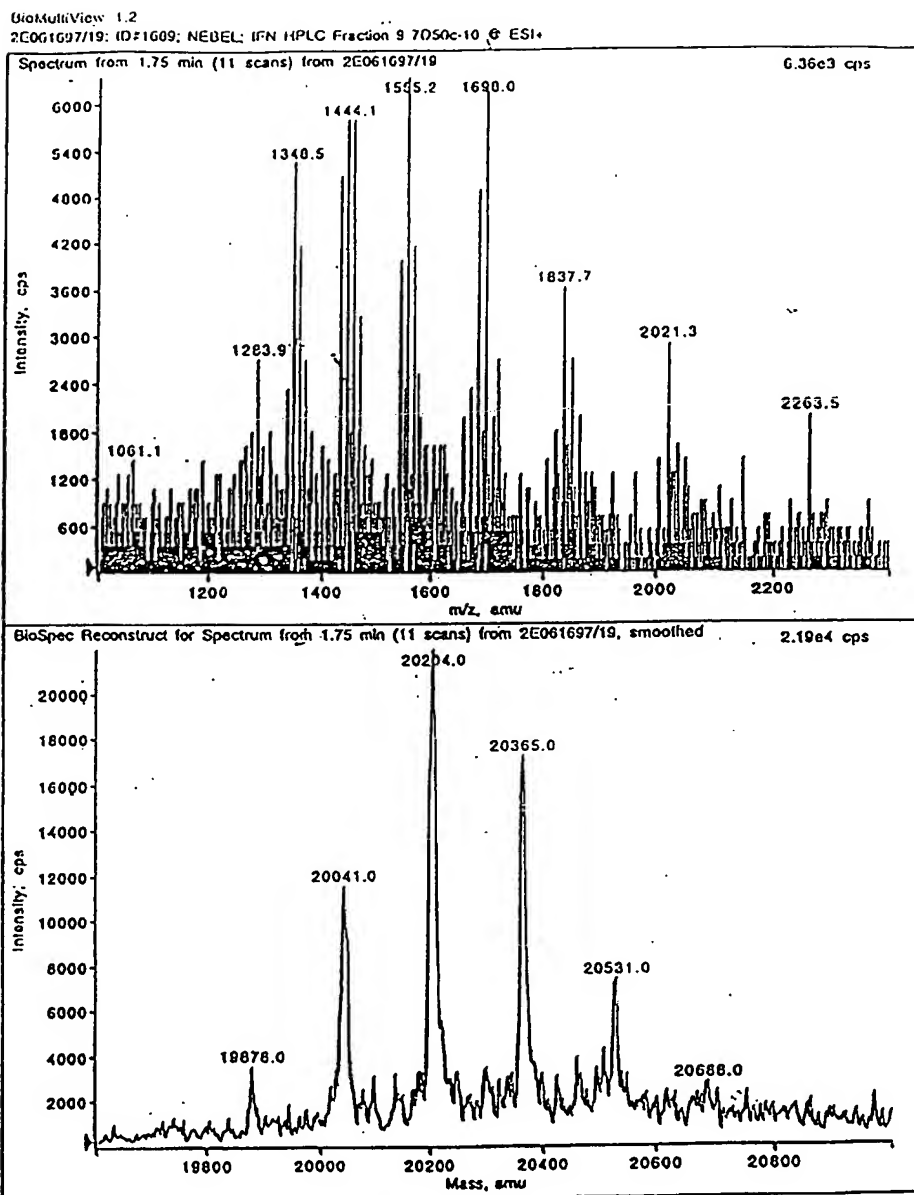


FIGURE 3

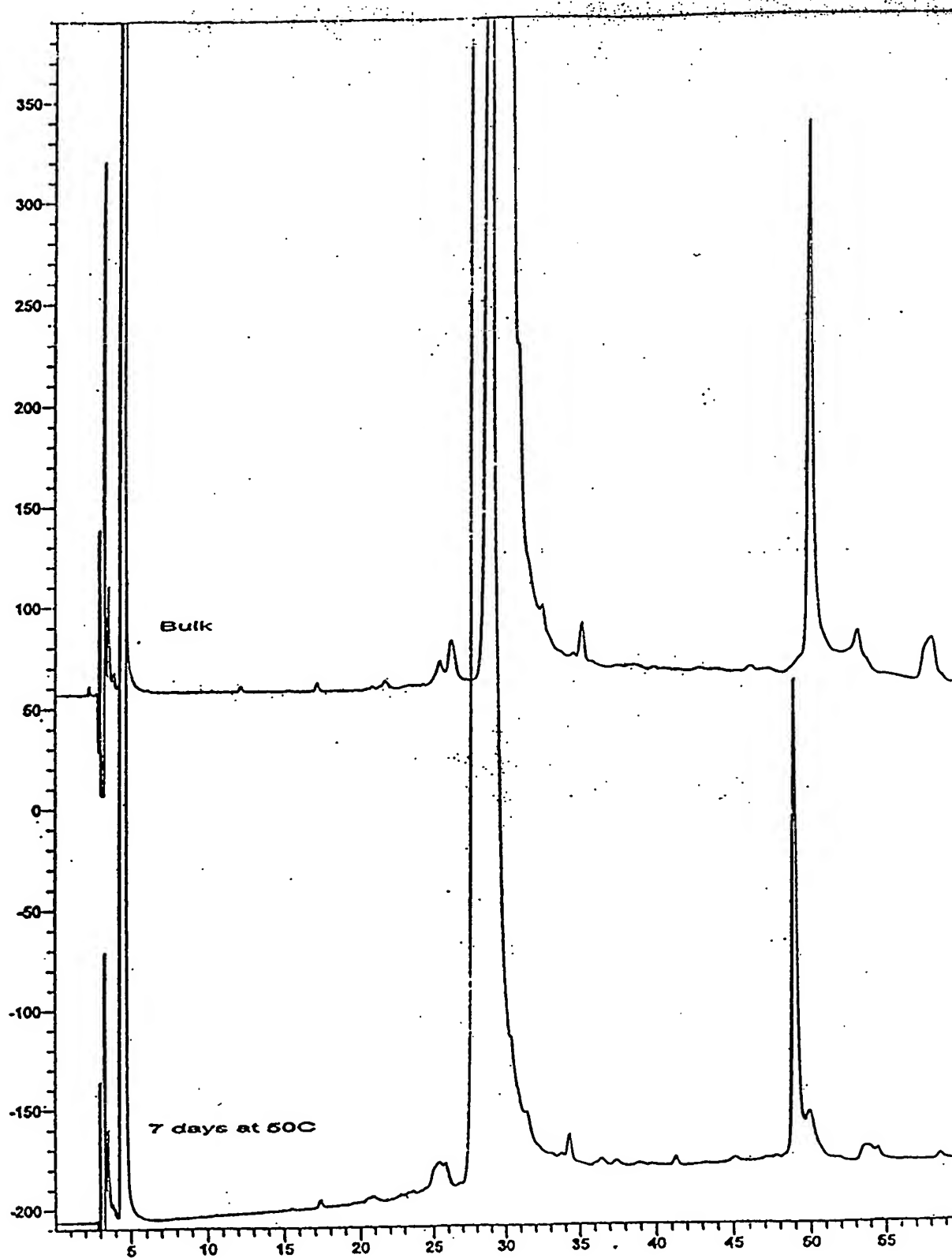


FIGURE 4

BioMutlView 1.2

2E061097/19: ID#1684; Nebol; 2a bulk 8 @ ESI+

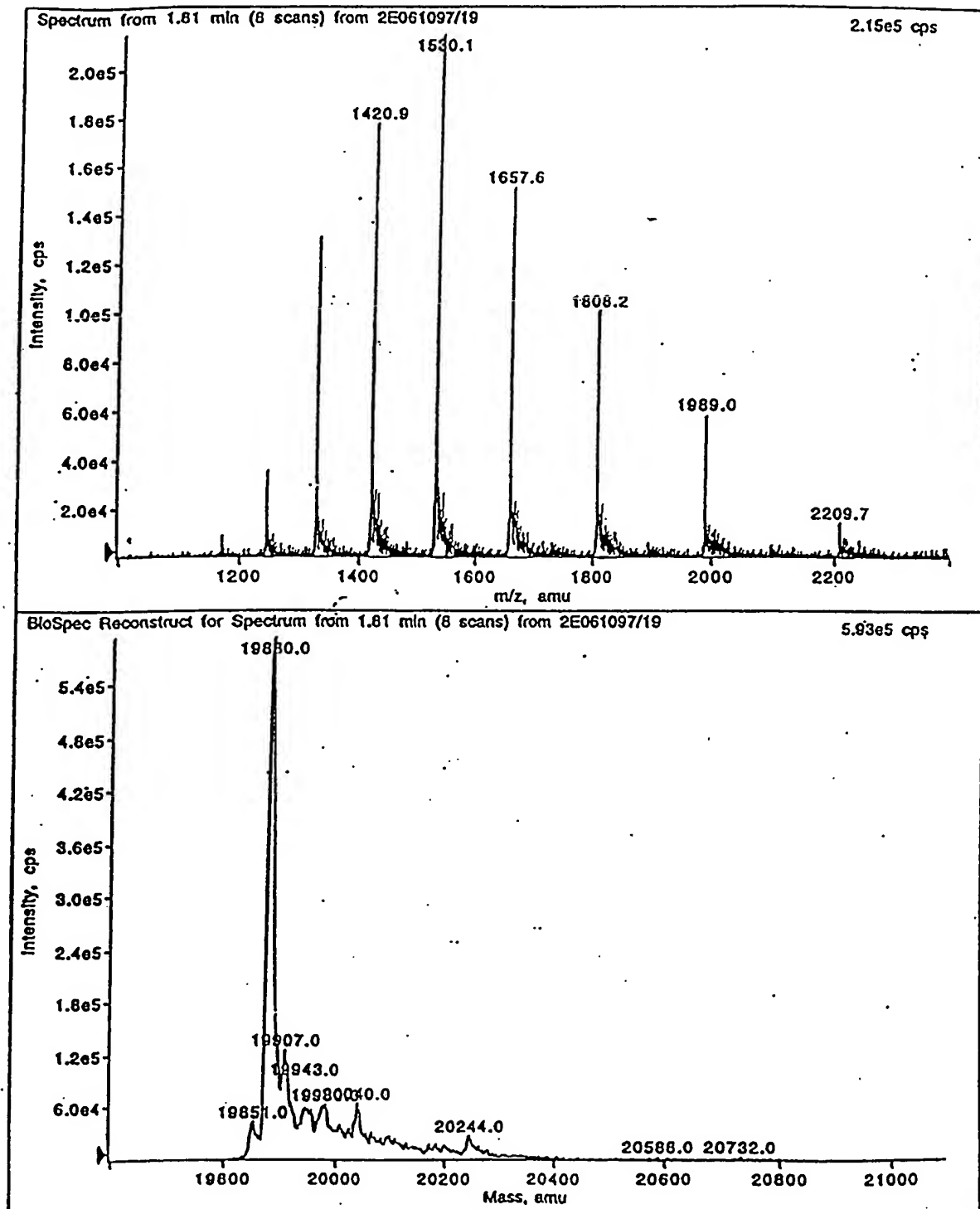


FIGURE 5

BioMultiView 1.2

2E061097/21: ID#1684; Nebel; 2e 7D50c 9 ESI+

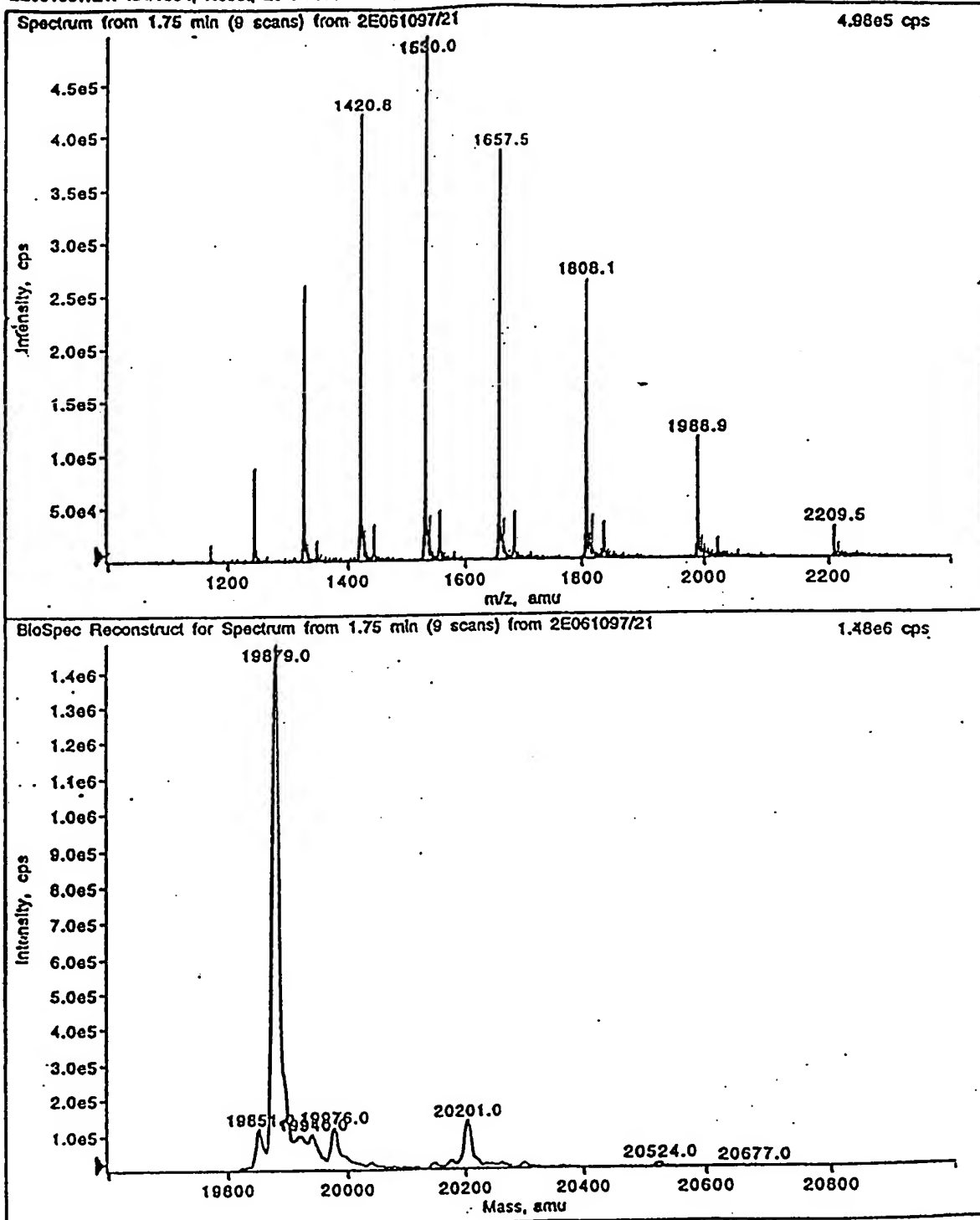


FIGURE 6

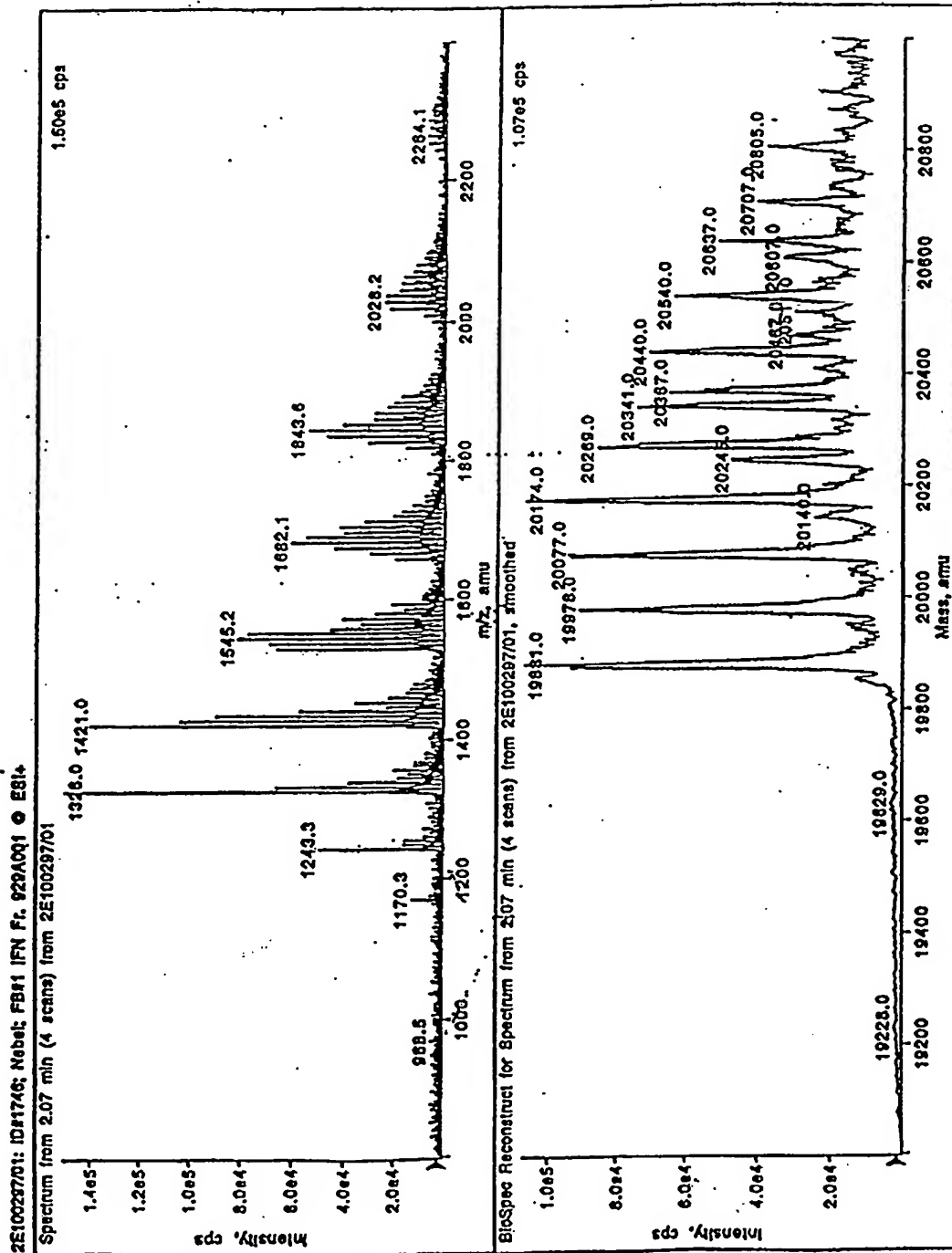


FIGURE 7

BioMultiView 1.2

2E10029704; 1D11746; Nebel; FB14 IFN-1 929A004.raw O ESI+

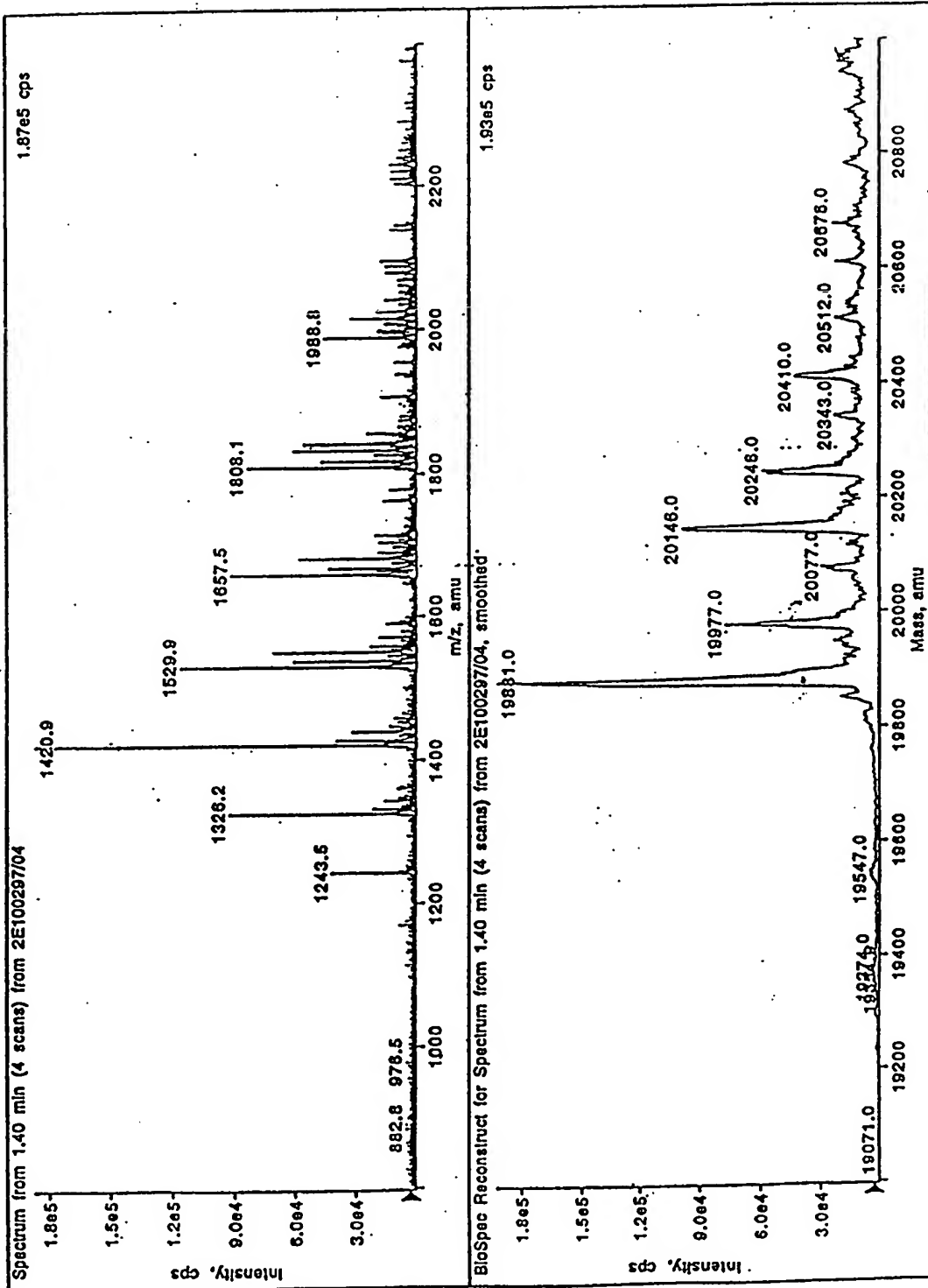


FIGURE 8

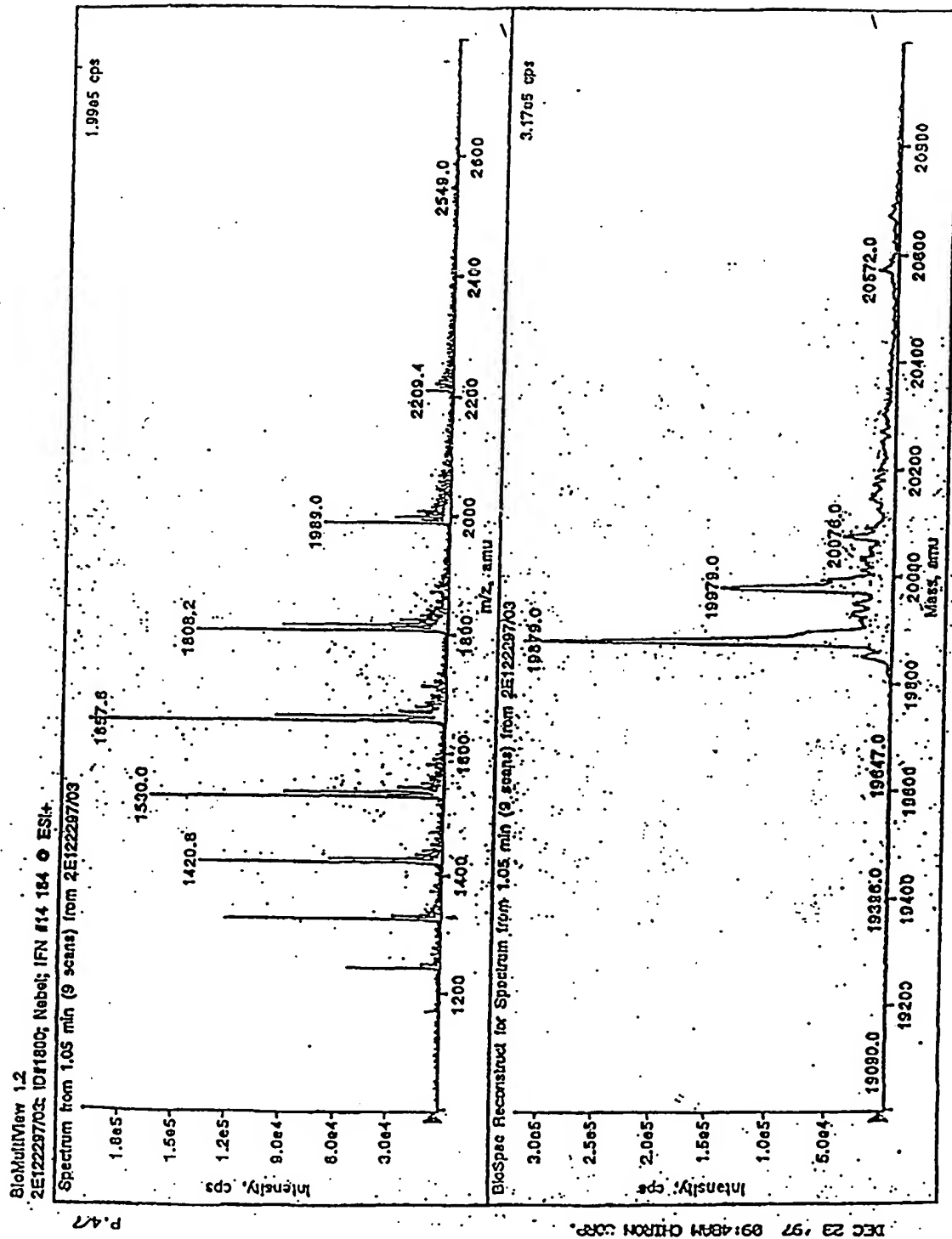


FIGURE 9

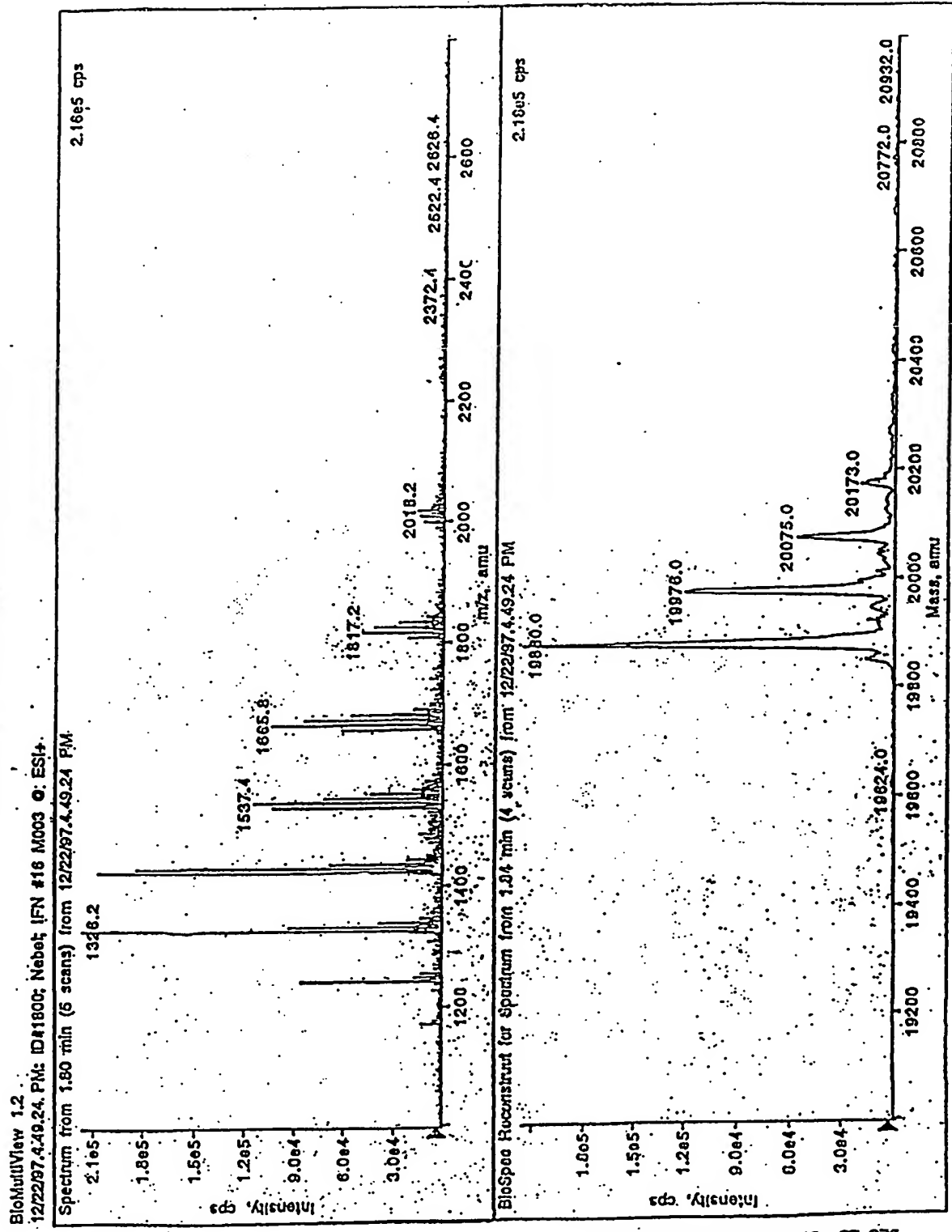


FIGURE 10

BioMolView, 1.2

2E122297/17: ID#1800; Nebel; IFN #17 5 © ESI+

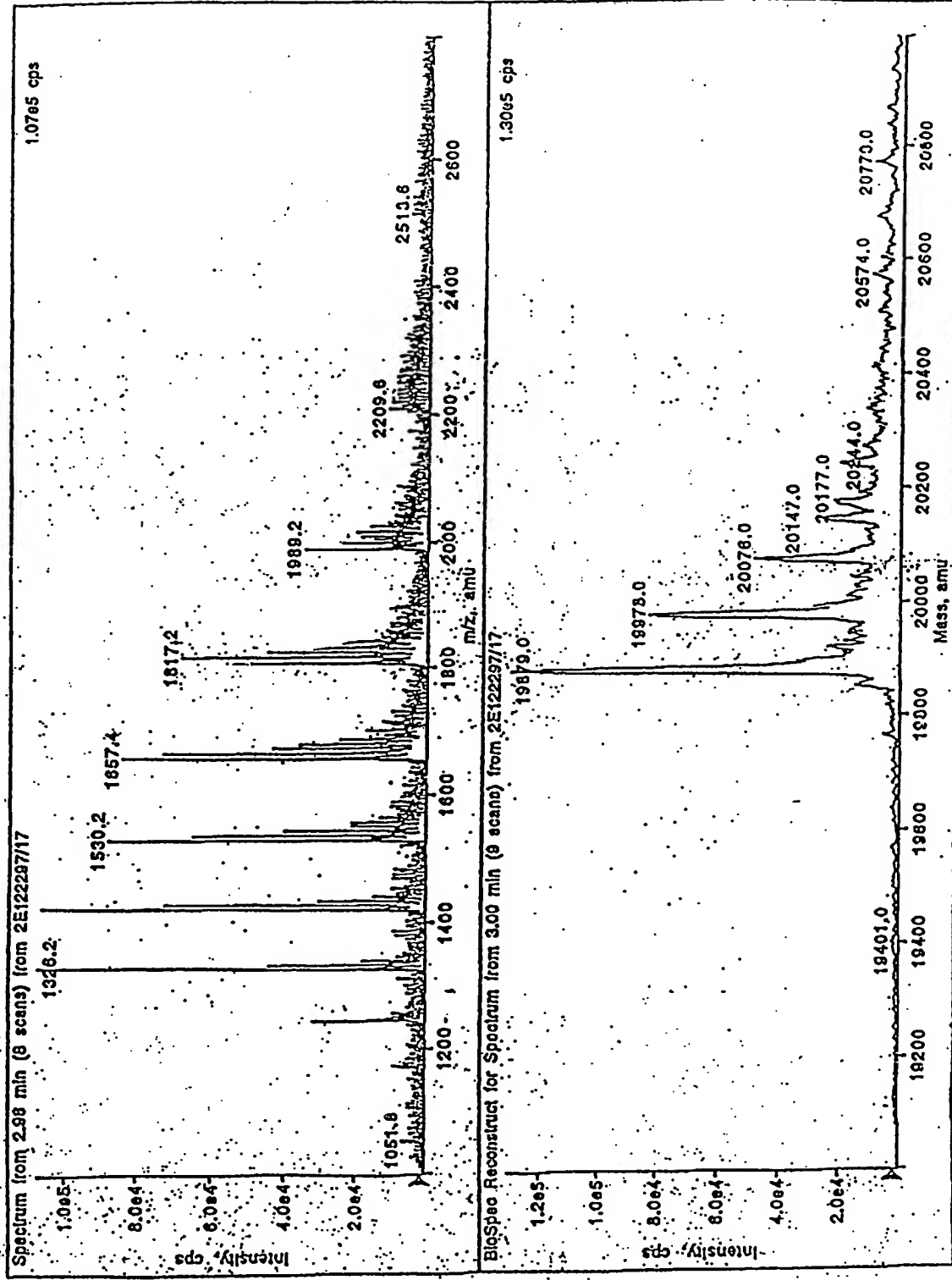


FIGURE 11

STABILITY EVALUATION DATA

Interferon- β -1b: Dextrose Formulation

Product	Storage Temperature (upright, protected from light)	Months	Potency (Specific activity, IU/mg)	Glucosylated IFN- β -1b concentration (mg/ml)	Total IFN β -1b concentration (mg/ml)
IFN- β 1b 0.25 mg/ml 1.25 % dextrose 1.25 % HSA Lot: MBAPM023 7200-607	+ 8°C	0	2.13×10^7	<0.02	0.22
	+ 8°C	1	2.50×10^7	<0.02	0.23
	+ 8°C	2	2.71×10^7	<0.02	0.23
	+ 50°C	2.2	3.52×10^7	<0.02	0.23
	+ 50°C	2.5	4.68×10^7	Too degraded	Too degraded
	+ 50°C	2.7	4.60×10^7	Too degraded	Too degraded
	+ 50°C	3	5.61×10^7	Too degraded	Too degraded
	+ 8°C	3	2.41×10^7	<0.02	0.23
IFN- β 1b 0.25 mg/ml 1.25 % dextrose 1.25 % HSA Lot: MBAPM027 7200-600	+ 25°C	0	2.12×10^7	<0.02	0.22
	+ 25°C	1	2.05×10^7	<0.02	0.21
	+ 25°C	2	3.24×10^7	<0.02	0.22
	+ 50°C	2.2	3.88×10^7	<0.02	0.21
	+ 50°C	2.5	4.64×10^7	Too degraded	Too degraded
	+ 50°C	2.7	5.08×10^7	Too degraded	Too degraded
	+ 50°C	3	5.91×10^7	Too degraded	Too degraded
	+ 25°C	3	2.51×10^7	<0.02	0.23
IFN- β 1b 0.25 mg/ml 1.25 % dextrose 1.25 % HSA Lot: MBAPM027 7200-600	+ 37°C	0	2.12×10^7	<0.02	0.22
	+ 37°C	1	2.85×10^7	<0.02	0.18
	+ 37°C	2	3.88×10^7	<0.02	0.23
	+ 50°C	2.2	4.28×10^7	Too degraded	Too degraded
	+ 50°C	2.5	4.88×10^7	Too degraded	Too degraded
	+ 50°C	2.7	4.72×10^7	Too degraded	Too degraded
	+ 50°C	3	5.44×10^7	Too degraded	Too degraded
	+ 37°C	3	4.08×10^7	Too degraded	Too degraded

FIGURE 12

STABILITY EVALUATION DATA

Interferon- β -1b: Highly Purified Mannitol Formulation

Product	Storage Temperature (upright, protected from light)	Months	Potency (Specific activity, IU/mg)	Glucosylated IFN- β -1b concentration (mg/ml)	Total IFN β -1b concentration (mg/ml)
IFN- β 1b 0.25 mg/ml 1.25 % highly purified mannitol 1.25 % HSA	+ 8°C	0	1.40×10^7	<0.02	0.22
	+ 8°C	1	1.52×10^7	<0.02	0.21
	+ 8°C	2	1.69×10^7	<0.02	0.22
	+ 50°C	2.2	1.68×10^7	<0.02	0.22
	+ 50°C	2.5	1.68×10^7	<0.02	0.21
	+ 50°C	2.7	1.54×10^7	<0.02	0.21
	+ 50°C	3	1.53×10^7	<0.02	0.22
	+ 8°C	3	1.62×10^7	<0.02	0.23
IFN- β 1b 0.25 mg/ml 1.25 % highly purified mannitol 1.25 % HSA	+ 25°C	0	1.40×10^7	<0.02	0.22
	+ 25°C	1	1.58×10^7	<0.02	0.21
	+ 25°C	2	1.88×10^7	<0.02	0.22
	+ 50°C	2.2	1.84×10^7	<0.02	0.22
	+ 50°C	2.5	1.67×10^7	<0.02	0.20
	+ 50°C	2.7	1.61×10^7	<0.02	0.21
	+ 50°C	3	1.53×10^7	<0.02	0.22
	+ 25°C	3	1.59×10^7	<0.02	0.23
IFN- β 1b 0.25 mg/ml 1.25 % highly purified mannitol 1.25 % HSA	+ 37°C	0	1.40×10^7	<0.02	0.22
	+ 37°C	1	1.50×10^7	<0.02	0.21
	+ 37°C	2	1.80×10^7	<0.02	0.21
	+ 50°C	2.2	1.86×10^7	<0.02	0.21
	+ 50°C	2.5	1.84×10^7	<0.02	0.20
	+ 50°C	2.7	1.73×10^7	<0.02	0.20
	+ 50°C	3	1.41×10^7	<0.02	0.20
	+ 37°C	3	1.53×10^7	<0.02	0.22

FIGURE 13

STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT
RESULTS FOR LOT MBDPN005 (MANNITOL FORMULATION)

Storage Temp. (°C)	Months in Storage	Appearance			Residual Moisture (% by weight)	pH Upon Reconstitution	Potency CPE/Blossary (IU/mg x 10 ⁷)	Container Closure Integrity Dye Leak Test	Sterility
		Phys. (color)	Upon Reconstitution	Upon Reconst. Clarity					
	0	white	clear, slightly yellow	-	0.3	7.4	2.3	-	Pass
4	2	-	-	-	0.4	-	-	-	-
4	3	white	clear, colorless	-	0.5	7.3	2.8	-	-
4	4	-	-	-	0.4	-	-	-	-
4	5	-	-	-	-	-	-	-	-
4	6	white	clear, colorless	-	0.4	7.3	3.4	-	-
4	9	white	clear, colorless	-	0.5	7.4	3.1	-	-
4	12	white	clear, colorless	-	0.5	7.5	3.2	-	-
4	18	white	clear, slightly yellow	II	0.6	7.4	3.3	-	-
4	24	white	clear, slightly yellow	<II	0.6	7.5	3.2	Pass	Pass
30	2	-	-	-	0.7	-	-	-	-
30	3	white	clear, colorless	<III	0.6	7.3	3.3	-	-
30	4	-	-	-	0.6	-	-	-	-
30	5	-	-	-	-	-	-	-	-
30	6	white	clear, slightly yellow	<III	0.7	7.4	3.1	-	-
30	9	white	clear, colorless	<III	0.8	7.5	3.1	-	-
30	12	white	clear, colorless	-	0.8	7.5	3.6	-	-
30	18	white	clear, slightly yellow	<III	1.0	7.4	2.8	-	-
30	24	white	clear, slightly yellow	<III	1.1	7.4	3.3	Pass	Pass
European Specifications:		White	Clear, colorless to light yellow	Not Ref III	Not > 3%	7.1-7.8	2.2 to 4.5 x 10 ⁷	Pass	Pass

FIGURE 14(A)

STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT
RESULTS FOR LOT MBDPN006 (MANNITOL FORMULATION)

Storage Temp. (°C)	Months in Storage	RP-HPLC Analysis	
		Interferon beta-1b (Peak B + Peak B1) (mg/ml)	Peak B1 (glucosylated) (mg/ml)
	0	-	-
4	2	-	-
4	3	-	-
4	4	-	-
4	5	-	-
4	6	0.24	<0.02
4	9	0.25***	<0.02***
4	12	0.23***	<0.02***
4	18	0.23	<0.02
4	24	0.25	<0.02
30	2	-	-
30	3	-	-
30	4	-	-
30	5	0.23	<0.02
30	6	0.25***	<0.02***
30	9	0.23***	<0.02***
30	12	0.23	<0.02
30	18	0.24	<0.02
30	24	0.24	<0.02
Expected Results:		0.25 ± 0.04	NMT 0.02

*** SOP QG162 (AKA Q1052) was not followed: NLT one injection per test vial (two test vials per lot) was not performed.

FIGURE 14(B)

STABILITY OF BETAFERON / BETAFERON FINAL CONTAINER PRODUCT
RESULTS FOR LOT NBDPN008 (MANNITOL FORMULATION)

Storage Temp. (°C)	Months in Storage	Pkg (cage)	Appearance			Residual Moisture (% by weight)	pH Upon Reconstitution	Potency CPE Blot assay (IU/mg x 10 ⁷)	Container Closure Integrity Dye Leak Test	Stability
			Upon Reconstitution	Upon Recon. Clarity	Upon Recon. Color					
	0	white	clear, colorless	-	-	0.3	7.3	2.9	-	Pass
4	2	-	-	-	-	0.5	-	-	-	-
4	3	white	clear, colorless	-	-	0.5	7.4	2.7	-	-
4	4	-	-	-	-	0.5	-	-	-	-
4	5	-	-	-	-	-	-	-	-	-
4	6	white	clear, colorless	-	-	0.5	7.5	3.3	-	-
4	9	white	clear, colorless	-	-	0.6	7.6	3.4	-	-
4	12	white	clear, colorless	-	-	0.6	7.6	3.2	-	-
4	18	white	clear, colorless	<III	colorless	0.6	7.5	2.8	-	-
4	24	white	clear, slightly yellow	<II	>BY ₇	0.6	7.6	3.3	Pass	Pass
30	2	-	-	-	-	0.7	-	-	-	-
30	3	white	clear, colorless	<III	-	0.7	7.5	3.0	-	-
30	4	-	-	-	-	0.6	-	-	-	-
30	5	-	-	-	-	-	-	-	-	-
30	6	white	clear, slightly yellow	<III	BY ₆	0.7	7.5	3.4	-	-
30	9	white	clear, colorless	II	<BY ₆	1.0	7.6	3.4	-	-
30	12	white	clear, colorless	-	-	0.9	7.6	3.2	-	-
30	18	white	clear, colorless	III	colorless	1.0	7.6	2.9	-	-
30	24	white	clear, slightly yellow	<III	>BY ₇	1.1	7.6	3.2	Pass	Pass
European Specifications			Clear, colorless to light yellow	NMT Ref III	Colorless to slightly yellow BY ₅	NMT 3%	7.1-7.8	2.2 to 4.5 x 10 ⁷	Pass	Pass

FIGURE 15(A)

STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT
RESULTS FOR LOT MBDPN008 (MANNITOL FORMULATION)

Storage Temp. (°C)	Months in Storage	RP-HPLC Analysis	
		Interferon beta-1b (Peak B + Peak B1)	Peak B1 (glucosylated) (mg/ml)
	0	-	-
4	2	-	-
4	3	-	-
4	4	-	-
4	5	0.23	<0.02
4	6	0.24***	<0.02***
4	9	0.23***	<0.02***
4	12	0.23	<0.02
4	18	0.24	<0.02
4	24	0.25	<0.02
30	2	-	-
30	3	-	-
30	4	-	-
30	5	0.23	<0.02
30	6	0.24***	<0.02***
30	9	0.22***	<0.02***
30	12	0.22	<0.02
30	18	0.23	<0.02
30	24	0.23	<0.02
Expected Results:		0.25 ± 0.04	NMT 0.02

*** SOP QG162 (AKA Q1052) was not followed; NLT one injection per test vial (two test vials per lot) was not performed
Note: A correction was made to the 18 month data point for RP-HPLC.

FIGURE 15(B)

STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT
RESULTS FOR LOT MBDEN009 (MANNITOL FORMULATION)

Storage Temp (°C)	Months in Storage	Plug (cable)	Appearance			Residual Moisture (% by weight)	pH Upon Reconstitution	Potency CPE Bioassay (IU/mg x 10 ⁷)	Container Closure Integrity Dye Leak Test
			Upon Reconstitution	Upon Reconst. Clarity	Upon Reconst. Color				
	0	white	clear, colorless	-	-	0.4	7.3	3.0	-
4	2	N/A	N/A	-	-	0.5	-	-	-
4	3	white	clear, colorless	-	-	0.5	7.3	2.9	-
4	4	N/A	N/A	-	-	0.5	-	-	-
4	5	N/A	N/A	-	-	-	-	-	-
4	6	white	clear, slightly yellow	-	-	0.4	7.3	2.3	-
4	9	white	clear, colorless	-	-	0.6	7.4	3.0	-
4	12	white	clear, colorless	-	-	0.5	7.4	3.1	-
4	18	white	clear, colorless	<III	colorless >BY ₁	0.8	7.5	2.9	-
4	24	white	clear, slightly yellow	<II	-	0.6	7.4	3.2	Pass
30	2	N/A	N/A	-	-	0.6	-	-	-
30	3	white	clear, colorless	-	-	0.6	7.3	3.2	-
30	4	N/A	N/A	-	-	0.6	-	-	-
30	5	N/A	N/A	-	-	-	-	-	-
30	6	white	clear, slightly yellow	-	-	0.5	7.4	2.4	-
30	9	white	clear, colorless	-	-	0.7	7.5	3.2	-
30	12	white	clear, colorless	-	-	0.7	7.4	3.1	-
30	18	white	clear, colorless	III	colorless >BY ₁	1.0	7.4	3.1	-
30	24	white	clear, slightly yellow	<III	-	1.0	7.4	3.3	Pass
European Specification			Clear, colorless to light yellow	NMT Ref III	Colorless to slightly yellow NMT BY ₁	NMT 3%	7.1-7.8	2.2 to 4.5 x 10 ⁷	Pass

FIGURE 16(A)

Title: Stabilized Interferon Compositions
 Inventor(s): Wolfe et al
 Application No: Not Assigned
 Atty Dkt No: PP16166.003(35784/240745)

STABILITY OF BETASERON / BETAFERON FINAL CONTAINER PRODUCT
 RESULTS FOR LOT MBDPN009 (MANNITOL FORMULATION)

Storage Temp. (°C)	Months in Storage	RP-HPLC Analysis	
		Interferon beta-1b (Peak B + Peak B1) (mg/ml)	Peak D1 (glycosylated) (mg/ml)
	0	-	-
4	2	-	-
4	3	-	-
4	4	-	-
4	5	-	-
4	6	0.24	<0.02
4	9	0.25***	<0.02***
4	12	0.24***	<0.02***
4	18	0.23	<0.02
4	24	0.25	<0.02
30	2	-	-
30	3	-	-
30	4	-	-
30	5	-	-
30	6	0.22	<0.02
30	9	0.25***	<0.02***
30	12	0.24***	<0.02***
30	18	0.23	<0.02
30	24	0.24	<0.02
30	24	0.24	<0.02

Expected Results: 0.25 ± 0.04 NMT 0.02
 *** SOP QG162 (AKA Q1052) was not followed: NLT one injection per test vial (two test vials per lot) was not performed
 Note: A correction was made to the 18 month data point for RP-HPLC.

FIGURE 16(B)

REDUCING ACTIVITY IN MANNITOL SAMPLES

Sample No.	Sample	Reducing Activity Content (ppm)	Mean Value (ppm)
1	Sample # 1 Unpurified	53.7	44.1
2	Sample # 2 Unpurified	44.1	
3	Sample # 3 Unpurified	34.4	
4	Sample # 1 Methanol Treated	19.3	18.5
5	Sample # 2 Methanol Treated	19.2	
6	Sample # 3 Methanol Treated	17.0	
7	Highly Purified Mannitol # 1	10.5	10.2
8	Highly Purified Mannitol # 2	11.2	
9	Highly Purified Mannitol # 3	8.9	

FIGURE 17